

From the INTERNATIONAL BUREAU

**PCT****NOTIFICATION CONCERNING  
TRANSMITTAL OF COPY OF INTERNATIONAL  
PRELIMINARY REPORT ON PATENTABILITY  
(CHAPTER I OF THE PATENT COOPERATION  
TREATY)**

(PCT Rule 44bis.1(c))

To:

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Date of mailing (*day/month/year*)

08 November 2007 (08.11.2007)

Applicant's or agent's file reference

NEREUS79VPC3

**IMPORTANT NOTICE**

International application No.

PCT/US2006/016104

International filing date (*day/month/year*)

27 April 2006 (27.04.2006)

Priority date (*day/month/year*)

29 April 2005 (29.04.2005)

Applicant

NEREUS PHARMACEUTICALS, INC. et al

The International Bureau transmits herewith a copy of the international preliminary report on patentability (Chapter I of the Patent Cooperation Treaty)

The International Bureau of WIPO  
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# PATENT COOPERATION TREATY

# PCT

## INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY (Chapter I of the Patent Cooperation Treaty)

(PCT Rule 44bis)

Applicant's or agent's file reference <b>NEREUS79VPC3</b>	<b>FOR FURTHER ACTION</b>	See item 4 below
International application No. <b>PCT/US2006/016104</b>	International filing date ( <i>day/month/year</i> ) <b>27 April 2006 (27.04.2006)</b>	Priority date ( <i>day/month/year</i> ) <b>29 April 2005 (29.04.2005)</b>
International Patent Classification (8th edition unless older edition indicated) See relevant information in Form PCT/ISA/237		
Applicant <b>NEREUS PHARMACEUTICALS, INC.</b>		

1. This international preliminary report on patentability (Chapter I) is issued by the International Bureau on behalf of the International Searching Authority under Rule 44 bis.1(a).

2. This REPORT consists of a total of 8 sheets, including this cover sheet.

In the attached sheets, any reference to the written opinion of the International Searching Authority should be read as a reference to the international preliminary report on patentability (Chapter I) instead.

3. This report contains indications relating to the following items:

- |                                     |              |   |
|-------------------------------------|--------------|---|
| <input checked="" type="checkbox"/> | Box No. I    | Basis of the report   |
| <input checked="" type="checkbox"/> | Box No. II   | Priority  |
| <input checked="" type="checkbox"/> | Box No. III  | Non-establishment of opinion with regard to novelty, inventive step and industrial applicability  |
| <input type="checkbox"/>            | Box No. IV   | Lack of unity of invention  |
| <input checked="" type="checkbox"/> | Box No. V    | Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement |
| <input checked="" type="checkbox"/> | Box No. VI   | Certain documents cited   |
| <input type="checkbox"/>            | Box No. VII  | Certain defects in the international application  |
| <input checked="" type="checkbox"/> | Box No. VIII | Certain observations on the international application   |

4. The International Bureau will communicate this report to designated Offices in accordance with Rules 44bis.3(c) and 93bis.1 but not, except where the applicant makes an express request under Article 23(2), before the expiration of 30 months from the priority date (Rule 44bis.2).

The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland	Date of issuance of this report <b>30 October 2007 (30.10.2007)</b>
Facsimile No. +41 22 338 82 70	Authorized officer <div style="text-align: center; font-weight: bold; margin-top: 10px;">Beate Giffo-Schmitt</div> e-mail: pt03.pct@wipo.int

# PATENT COOPERATION TREATY

From the  
INTERNATIONAL SEARCHING AUTHORITY

To:

see form PCT/ISA/220

# PCT

## WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY (PCT Rule 43bis.1)

Date of mailing  
(day/month/year) see form PCT/ISA/210 (second sheet)

Applicant's or agent's file reference  
see form PCT/ISA/220

**FOR FURTHER ACTION**  
See paragraph 2 below

International application No.  
PCT/US2006/016104

International filing date (day/month/year)  
27.04.2006

Priority date (day/month/year)  
29.04.2005

International Patent Classification (IPC) or both national classification and IPC  
INV. A61K31/407 A61P35/00

Applicant  
NEREUS PHARMACEUTICALS, INC.

**1. This opinion contains indications relating to the following items:**

- ☒ Box No. I Basis of the opinion
- ☒ Box No. II Priority
- ☒ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☐ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Rule 43bis.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- ☒ Box No. VI Certain documents cited
- ☐ Box No. VII Certain defects in the international application
- ☒ Box No. VIII Certain observations on the international application

**2. FURTHER ACTION**

If a demand for international preliminary examination is made, this opinion will usually be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA") except that this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notified the International Bureau under Rule 66.1bis(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of 3 months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

**3. For further details, see notes to Form PCT/ISA/220.**

Name and mailing address of the ISA:



European Patent Office  
D-80298 Munich  
Tel. +49 89 2399 - 0 Tx: 523656 epmu d  
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Date of completion of  
this opinion

see form  
PCT/ISA/210

Authorized Officer

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**WRITTEN OPINION OF THE  
INTERNATIONAL SEARCHING AUTHORITY**

International application No.  
PCT/US2006/016104

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**Box No. I Basis of the opinion**

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1. With regard to the **language**, this opinion has been established on the basis of:
  - ☒ the international application in the language in which it was filed
  - ☐ a translation of the international application into , which is the language of a translation furnished for the purposes of international search (Rules 12.3(a) and 23.1 (b)).
2. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of:
  - a. type of material:
    - ☐ a sequence listing
    - ☐ table(s) related to the sequence listing
  - b. format of material:
    - ☐ on paper
    - ☐ in electronic form
  - c. time of filing/furnishing:
    - ☐ contained in the international application as filed.
    - ☐ filed together with the international application in electronic form.
    - ☐ furnished subsequently to this Authority for the purposes of search.
3. ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.
4. Additional comments:

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**Box No. II Priority**

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1. ☐ The validity of the priority claim has not been considered because the International Searching Authority does not have in its possession a copy of the earlier application whose priority has been claimed or, where required, a translation of that earlier application. This opinion has nevertheless been established on the assumption that the relevant date (Rules 43bis.1 and 64.1) is the claimed priority date.
2. ☒ This opinion has been established as if no priority had been claimed due to the fact that the priority claim has been found invalid (Rules 43bis.1 and 64.1). Thus for the purposes of this opinion, the international filing date indicated above is considered to be the relevant date.
3. Additional observations, if necessary:

**WRITTEN OPINION OF THE  
INTERNATIONAL SEARCHING AUTHORITY**

International application No.  
PCT/US2006/016104

**Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability**

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non obvious), or to be industrially applicable have not been examined in respect of

☐ the entire international application

☒ claims Nos. 1-29

because:

☒ the said international application, or the said claims Nos. 1-29 relate to the following subject matter which does not require an international search (*specify*):

**see separate sheet**

☐ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. are so unclear that no meaningful opinion could be formed (*specify*):

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed (*specify*):

☐ no international search report has been established for the whole application or for said claims Nos.

☐ a meaningful opinion could not be formed without the sequence listing; the applicant did not, within the prescribed time limit:

☐ furnish a sequence listing on paper complying with the standard provided for in Annex C of the Administrative Instructions, and such listing was not available to the International Searching Authority in a form and manner acceptable to it.

☐ furnish a sequence listing in electronic form complying with the standard provided for in Annex C of the Administrative Instructions, and such listing was not available to the International Searching Authority in a form and manner acceptable to it.

☐ pay the required late furnishing fee for the furnishing of a sequence listing in response to an invitation under Rules 13ter.1(a) or (b).

☐ a meaningful opinion could not be formed without the tables related to the sequence listings; the applicant did not, within the prescribed time limit, furnish such tables in electronic form complying with the technical requirements provided for in Annex C-bis of the Administrative Instructions, and such tables were not available to the International Searching Authority in a form and manner acceptable to it.

☐ the tables related to the nucleotide and/or amino acid sequence listing, if in electronic form only, do not comply with the technical requirements provided for in Annex C-bis of the Administrative Instructions.

☐ See Supplemental Box for further details

**WRITTEN OPINION OF THE  
INTERNATIONAL SEARCHING AUTHORITY**

International application No.  
PCT/US2006/016104

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**Box No. V Reasoned statement under Rule 43bis.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement**

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1. Statement

Novelty (N)	Yes: Claims	1-29
	No: Claims	
Inventive step (IS)	Yes: Claims	1-29
	No: Claims	
Industrial applicability (IA)	Yes: Claims	
	No: Claims	

2. Citations and explanations

see separate sheet

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**Box No. VI Certain documents cited**

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1. Certain published documents (Rules 43bis.1 and 70.10)

and / or

2. Non-written disclosures (Rules 43bis.1 and 70.9)

see form 210

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**Box No. VIII Certain observations on the international application**

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The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

see separate sheet

- 1) The present application relates to the use of heterobicyclic compounds of formula VI-A or VI in treatment of rectal cancer.
- 2) Cited documents  
D1: WO 2004/071382 A  
D2: WO 96/32105 A  
D3: US 2005/288352 A1 (2005-12-29)  
D4: WO 2006/028525 A(2006-03-16)  
D5: J.ORG.CHEM., vol. 70, no. 16, (2005-07-01), pages 6196-6203  
D6: WO 2006/060609 A (2006-06-08)

Documents D3-D5 were published after the priority claimed for the present application and are herein only considered as prior art in as far as the application is not priority entitled.

Document D6 was published after the filing of the present application and is herein not considered as prior art. Document D6 results from the priority application.

3) Priority

The compounds of formula VI-A are not described in the priority document. Moreover, compounds of formula VI-1B and VI-1C as defined in the present application had not been described in the priority document with similar stereochemistry and can therefore not be regarded as specifically disclosed in the priority document. Finally, whereas the priority document may be regarded to describe compounds of formula VI, VI-1 and VI-1A as presently defined for treatment of rectal cancer, these documents do not appear to specifically describe the use of these agents to induce apoptosis of a cancer cell wherein the cancer cell is rectal cancer.

In as far as the claimed subject-matter is not specifically disclosed in the priority document, the priority cannot be recognized.

3) Novelty

Document D1 describes various salinosporamides as proteasome inhibitors useful in the treatment of a variety of disorders, including colon cancer (see pages 19-20). This document does not disclose the alternatively fused compounds presently defined and does not specifically describe treatment of rectal cancer.

Document D2 describes lactacystin analogues useful as proteasome inhibitors; the compounds of D2 lack the substitution "R3" in the compounds presently defined.

Documents D3 and D4 already describe compounds of formula VI, VI-1 and VI-1A and specific stereoisomers of formula VI-1B and VI-C as useful in treatment of i.a. colorectal carcinoma. These documents do not specifically describe treatment of rectal cancer, which may be considered a specific subgroup within colorectal cancer.

Document D5 describes activity of a compound of formula VI/VI-1 as active against colon cancer cells; the document does not describe treatment of rectal cancer.

4) Inventive step

In as far as the claimed subject-matter is priority entitled, document D1 may be considered as closest prior art.

The alternatively fused agents as presently defined would however seem obvious, active derivatives from the known salinosporamides of D1 in the light of D3, as this document D3 describes for the structurally and functionally closely related lactacystins the possibility of similar, alternative fusion (see meaning of Z2/R1/R2 on i.a. page 2). The selection of rectal cancer would in this context appear an obvious selection amongst types of susceptible cancer, especially in the light of colon cancer as mentioned susceptible cancer.

In as far as the priority is not valid, documents D3-D5 represent additional prior art describing activity of compounds of formula VI, VI-1 and VI-1A and specific stereoisomers of formula VI-1B and VI-C as useful in treatment of cancer such as colorectal carcinoma. The selection of treatment of rectal cancer would in the light of D3-D5 seem an obvious selection amongst types of susceptible cancer.

Moreover, the further modification implied by the definition of compounds by formula VI-A (additional substitution by R1) would seem obvious by analogy with the general formula for the alternatively fused salinosporamides known to be similarly active (D3/D4, formula I).

In this context it is further observed that the application appears to provide no specific support for particular activity of compounds of formula VI-A nor particular



activity against rectal cancer.

5) Further observations

- 5.1 The compounds of formula VI-1A/B/C of claim 7 do not appear covered by the independent claim 1 relating to compounds of formula VI-A (in which R1 is not hydrogen) alternatively fused salinosporamides of dependent claims 6, 17, 28, 46 and 64 would not appear to fall under the respective independent claims.
- 5.2 Claims 1-29 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(I) PCT).
- 5.3 The claims relate to heterobicyclic compounds of formula VI-A or VI, whereas the description refers the invention as pertaining to alternatively fused salinosporinamides as well.